Carvedilol treatment of chronic heart failure: a new era

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The adrenergic hypothesis of heart failure was formulated in the early 1980s when it was first appreciated that myocardial failure and end stage heart disease in man was accompanied by increased cardiac adrenergic drive and impaired β adrenergic signal transduction.[1 2]

Cardiac adrenergic drive has been shown to increase even during the earliest stages of asymptomatic left ventricular dysfunction.[3] This is a local effect that occurs before any other neurohormonal perturbation, as shown by increased release of noradrenaline within the heart without an accompanying increase in circulating noradrenaline levels.

One of the first biological consequences of chronic adrenergic stimulation is widespread alterations in β receptor signal transduction, including a 50–60% downregulation of myocardial β_1 adrenoceptors.[4–7] This and other β receptor pathway desensitisation phenomena reduce myocardial reserve, which in turn decreases the ability of the heart to function under stress, and contributes to the loss in maximal exercise performance in patients with heart failure. The second general biological consequence of chronic adrenergic stimulation is progressive myocardial dysfunction, which is related to adverse effects of noradrenaline on cardiac myocytes or the myocardium in general. This component of the adrenergic hypothesis is based on the clinical observation that β adrenoceptor blockade prevents, and actually reverses, progressive myocardial dysfunction.[7]

Role of β adrenoceptors

The possibility of a direct connection between altered β adrenoceptor signal transduction and progressive myocardial dysfunction has been shown in transgenic animal models overexpressing human β adrenergic receptors[8] or a dominant negative peptide that inhibits β adrenoceptor kinase activity.[9] Under these experimental conditions, the expression of β adrenoceptors or augmentation of receptor function directly affects myocardial contractility.[8 9] However, it is not known whether the β receptor-signal transduction alterations that occur in the failing human heart directly alter intrinsic contractile function.

Patients with heart failure have a downregulation of β_1 adrenoceptors without any change in β_2 adrenoceptor density.[4–7] There are also mild changes in β_2 adrenoceptor function.[10] α_1 Adrenoceptor density is low in the normal myocardium and increases in heart failure,[11 12] and angiotensin II AT_1 receptors, which have

an even lower density than α_1 adrenoceptors, downregulate.[13 14]

Downregulation of α_1 adrenergic receptor density is thought to be related to an increase in specific binding proteins that destabilise the receptor mRNA and shorten its half life.[13 14] The selective loss of most of the population of β_1 adrenoceptors that occurs in patients with idiopathic dilated or ischaemic cardiomyopathy results in a relative increase in the proportion of β_2 adrenoceptors.[4–6 15] Thus, in the failing human heart a substantial proportion (about 35–40%) of the total β receptor population is β_2.[4–6 15]

Role of β blockers

Three different generations of β blocking agents have been developed.[16] The prototype agent was propranolol, which is a non-selective agent with high affinity for β_1 and β_2 adrenoceptors and no affinity for α_1 adrenoceptors.

The second generation β blockers, typified by metoprolol, were developed to be selective for β_1 adrenoceptors with the aim of reducing peripheral or pulmonary side effects. Metoprolol is approximately 80 times more selective for human myocardial β_1 adrenoeceptors than for β_2 adrenoceptors. Another second generation compound that has been used to treat heart failure, bisoprolol, is about 120 times more selective for β_1 than β_2 receptors. These second generation agents do not affect α adrenoceptors.

The third generation, vasodilating β blockers, such as carvedilol and bucindolol, were specifically developed as antihypertensive agents. At clinically effective doses, carvedilol possesses only slight (about sevenfold) β adrenoceptor selectivity[17] but it has fairly potent α_1 adrenoceptor blocking properties.[17 18] Indeed its affinity for α_1 adrenoceptors is one third its affinity for β_1 adrenoceptors.[18] Thus, there is good evidence that carvedilol acts as an antagonist at all three adrenergic receptors (β_1, β_2, and α_1 adrenoceptors). In the failing heart these receptors exist in a ratio of 2:1:1.[19]

The vasodilator properties of carvedilol mean that, despite its lack of β selectivity, it can be given acutely at low doses to patients with congestive heart failure.[20–22] Bucindolol has relatively weaker vasodilator properties, which probably are not caused by α blockade, but are related to a "direct" vasodilator effect.[23 24] Similar to carvedilol, the non-selective agent bucindolol can be tolerated by patients with chronic heart failure,[25 26] whereas

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first generation, non-selective agents, which are devoid of vasodilator activity, are poorly tolerated.[27]

Mechanism of action of carvedilol

There is ample evidence to show that the anti-adrenergic mechanism of action of carvedilol differs from that of metoprolol. In one recent comparative study, coronary sinus noradrenaline concentrations tended to increase after six months of treatment with metoprolol, whereas with carvedilol there was a significant decrease in noradrenaline compared with baseline, placebo treatment, and the change in the metoprolol group.[28] In the same study, β adrenoceptor density studies performed on myocardial biopsy specimens taken from patients treated with metoprolol showed upregulation caused by an increased density of the β_1 subtype, which are receptors that are downregulated in heart failure. With carvedilol there was no change in β adrenoceptor density.

In vitro studies have shown that incubation of cardiac or other cell types with carvedilol results in a downregulation of β_1 or β_2 adrenoceptors, whereas metoprolol produces a significant upregulation of receptors (unpublished data).[26] These direct effects of carvedilol and metoprolol on receptor protein expression are presumably the explanation for the receptor effects observed in the failing human heart.[28]

In the metoprolol-carvedilol comparative study,[28] the complete dissociation between change in receptor density and the improvement in left ventricular function observed for carvedilol treated patients suggests that the salutary effects of carvedilol on left ventricular function are not mediated by regulation of β adrenoceptor density or restoration of signal transduction. The implications of this finding are that, compared with second generation compounds, carvedilol has additional anti-adrenergic effects that contribute to its clinical efficacy.[29]

Vasodilating properties of carvedilol

When administered acutely to subjects with heart failure, carvedilol has moderate vasodilating properties. It reduces pulmonary artery wedge pressure and decreases systemic vascular resistance.[30] The reduction in systemic vascular resistance unloads the ventricle and stabilises or increases cardiac output, counteracting the myocardial depressant effects of withdrawing adrenergic support to the failing heart.

Standard measurement of left ventricular function using right heart catheterisation data were undertaken as part of our initial carvedilol trial.[21] After four months of treatment with carvedilol there was an upward left shift in the curve of stroke volume index versus wedge pressure, indicating that stroke volume index had increased and pulmonary wedge pressure had decreased.[21] However, there was no change in systemic vascular resistance.[21] This suggests that the left ventricular functional effects were caused by improved intrinsic systolic function rather than the indirect effects of afterload reduction. Likewise, in a three-way comparison between bucindolol, carvedilol, and metoprolol, we found that systemic vascular resistance effects of carvedilol were not different from those of metoprolol, indicating that with time there appears to be an attenuation or even a loss of the acute vasodilator properties of carvedilol.

A placebo controlled study investigating changes in systolic and diastolic function and volume showed a 40% increase in left ventricular ejection fraction after four months of treatment with carvedilol.[31] Systolic and diastolic volumes were reduced in the carvedilol group, compared with a slight increase in the placebo group. However, radionuclide determinations of peak filling rate and time to peak filling rate failed to provide evidence of a favourable affect on diastolic function.[31] These data suggest that the primary effect of carvedilol is on systolic rather than diastolic function. More recent data indicate that carvedilol improves both right and left ventricular function in subjects with idiopathic dilated or ischaemic cardiomyopathy.[32]

Remodelling studies

The size and shape of the ventricle has obvious consequences for cardiac function. In Western societies the most common cause of ventricular dysfunction is a previous myocardial infarction. In the early stages that follow infarction, ventricular geometry remains unchanged and the non-infarcted areas of the myocardium contract normally. Myocyte dysfunction develops progressively in these non-infarcted areas and remodelling occurs, first at the cellular level as seen by myocyte elongation and then at the level of the ventricle itself, which becomes dilated and more spherical. Both the renin-angiotensin system and the adrenergic systems participate in this process.[33]

Cross sectional echocardiography studies indicate that the ratio between the long and short axes of the ventricle approaches unity as the ventricle becomes more spherical as a result of the remodelling process that accompanies progressive left ventricular dysfunction. Carvedilol is able to reverse these changes and actually enables the ventricle to elongate so that it approaches a more normal shape.[34] After four months of treatment there is a slight decrease in left ventricular mass that is not significant compared to baseline but is significant compared to placebo treated patients in whom there is an increase.[34] Analysis after 12 months of treatment shows a profound reduction in left ventricular mass in heart failure patients with both ischaemic and idiopathic dilated cardiomyopathy. This is accompanied by geometric normalisation of the chamber.[34]

These findings indicate that the acute pharmacological effect of β blockade, which is myocardial depression owing to loss of adrenergic support to the failing heart,[35] can be counteracted by the vasodilator properties of third generation β blockers. However, over

time, the acute negative inotropic effects of β blockers converts to improved biological function and structure of the dilated, failing heart. Thus, the real objective of using drugs such as carvedilol to treat heart failure is not based on their pharmacological properties per se, but rather on their ability to alter favourably the biology of the failing ventricle. The implication is that if cardiac function can be improved by such a biological effect, then this treatment should improve the natural history of heart failure.

Effects on natural history of heart failure

Carvedilol has been shown to cause dose related improvements in left ventricular ejection fraction.[36] In this six month study, there were only 25 deaths among 345 patients, and the reduction in mortality was also dose related; only one death occurred with high dose carvedilol.[36] These data suggest that the effect of carvedilol of improving the biological properties of the failing heart is translated into a beneficial effect on the natural history of heart failure.

Combined analysis of the US carvedilol heart failure study programme also showed a highly significant reduction in mortality in patients treated with carvedilol.[37] The Australia-New Zealand study showed clear evidence of long term benefit on morbidity and mortality beyond six months.[38]

Conclusions

β Blocking agents have a biphasic effect on myocardial function and clinical symptoms in subjects with chronic heart failure resulting from systolic dysfunction. As the heart is withdrawn from adrenergic support, the acute pharmacological effect of β blockade is myocardial depression. However, the vasodilator properties of carvedilol are able to counteract much of the decrease in cardiac output associated with acute administration of first or second generation β blockers.

After one to three months of treatment with carvedilol, or other well tolerated β blocking agents, there is an improvement in intrinsic systolic function coupled with a reduction in systolic and diastolic volume, and an improvement in ejection fraction. These time dependent effects are diametrically opposite to the acute pharmacological response to β blockade.

After four to 12 months of treatment with carvedilol, left ventricular mass decreases, chamber shape becomes more elliptical, and mitral regurgitation lessens. These effects are a reversal of remodelling, similar to that described for metoprolol.[39]

The changes in intrinsic systolic function, ventricular volume, mass and chamber characteristics represent an improvement in the biological properties of the failing heart. The mechanisms that underlie this change in biological function almost certainly involve alterations in gene expression towards a more normal phenotype.

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